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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/803,854	03/12/2001	Albert J. Wong	WON01-NP003	1297

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EXAMINER	
CHEU, CHANGHWA J	
ART UNIT	**PAPER NUMBER**
1641	

DATE MAILED: 06/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/803,854	WONG ET AL.	
	Examiner	Art Unit	
	Jacob Cheu	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11 and 21-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1, 3, 5, 6, 9, 11, 21-25* is/are rejected.

7)☒ Claim(s) *2,4,7 and 8* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on 2/20/2004 has been received and entered into record and considered.

The following information provided in the amendment affects the instant application:

1. Claims 12-20 arre cancelled.
2. Claims 21-25 are added to the instant application.
3. Currently, claims 1-11 and 21-25 are under examination.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

2. Claims 5, 10, 11 and 21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant specification does not contain a written description of the invention in such full, clear, concise, and exact terms or in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing.

The claims are drawn to detect certain cancers by using the mutant EGFRvIII as a indicator. The specification disclose that "using a polyclonal anti EGFRvlll-specific antibody, Moscatello, Wong, and colleagues have detected this mutant protein in 16% of non-small cell lung tumors, 78% of breast carcinomas, 57% of primary human glial tumors, 86% of medulloblastoma tumors, and 75% of ovarian tumors (7-9). Furthermore, the EGFRvIII is tumor specific, since it is not detected in any normal tissue examined (7-10)" (See page 3, second paragraph). Although elevated levels of normal EGFR have been reported in many human tumors and cell lines, including breast cancer, adenocarcinoma and squamous lung cancer, gastrointestinal cancers (gastric, colon, pancreatic), renal cell cancer, bladder cancer, glioma, gynecological carcinomas, and prostate cancer (page 2, third paragraph). The specification does not have support that the elevated levels of *mutant EGFRvIII* are associated with the similar cancers like normal EGFR.

The instant specification fails to provide sufficient descriptive information as to how the normal EGFR shares same characteristics with the mutant EGFRvIII in associating with the gastrointestinal cancer, renal cell cancer, bladder cancer, Barrett's and prostate cancer. Applicant's specification provides support for the elevated normal EGFR, not the mutant EGFRvIII as recited in claims 5, 10, 11 and 21. Accordingly, one of skill in the art would reasonably conclude that applicant does not possess the invention other than the specified mutant EGFRvIII related cancers, such as gastrointestinal cancer, renal cell cancer, bladder cancer, and prostate cancer.

Enablement

3. Claims 24 and 25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described

in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As set forth in *In re Wands, 858 F .2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)*, enablement requires that the specification teach those skilled in the art to make and use the invention without undue experimentation. Factors to be considered in determining, whether a disclosure would require undue experimentation include 1) the nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the quantity of experimentation necessary, 7) the relative skill of those in the art, and 8) the breadth of the claims.

Applicant shows how to make and purify instant EGFRvIII specific antibody that does not cross react with wild type (wt) EFGR. (page 6, last paragraph to page 7, first paragraph) The procedure provide guidance instructing one skilled in the art (1) passing the antibodies mixture (containing both antibodies against EGFR and mutant EGFRvIII) to an affinity column coated with peptide SEQ ID No. 2, and (2) "[t]he flow through from this column was then *passed* over an affinity column containing peptide SEQ ID No. 3." The final "*flow-through* antibody recognized only EGFRvIII, whereas the antibodies *bound* to SEQ ID No. 2 and 3 columns, cross-react with the normal EGFR. (page 6, first paragraph) It is this "flow-through" (i.e. not bound) antibody possessing this anti-EGFRvIII activity, not the adsorption of either SEQ ID No. 2 or 3, renders specificities. Note, according to the experimental guidance, it requires two peptides (SEQ ID No. 2 and 3), not either one alone, to make this EGFRvIII specific antibody.

In view of the aforementioned lack of predictability in the art, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in the applicant's specification of how to effectively practice the recited method and absent working examples.

Scope of Enablement

4. Claims 5, 10, 11, and 21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for non-small cell carcinoma, breast carcinoma, glial tumor, ovarian tumors, does not reasonably provide enablement for gastrointestinal cancer, renal cell cancer, bladder cancer, Barrett's and prostate cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

As discussed before, the instant invention is drawn to detect certain cancers by using the mutant EGFRvIII as a indicator. The specification disclose that "using a polyclonal anti EGFRvlll-specific antibody detect this mutant protein and found out positive correlation to non-small cell lung tumors (16%), breast carcinomas (78%), primary human glial tumors (57%), medulloblastoma tumors (86%), and 75% of ovarian tumors. (See page 3, second paragraph) Although elevated levels of EGFR have been reported in many human tumors and cell lines, including breast cancer, adenocarcinoma and squamous lung cancer, gastrointestinal cancers (gastric, colon, pancreatic), renal cell cancer, bladder cancer, glioma, gynecological carcinomas, and prostate cancer. (page 2, third paragraph) The specification does not have support that the elevated levels of mutant EGFRvIII are associated with the similar cancers like normal EGFR. It is clear that both EGFR and mutant EGFRvIII are structurally and functional distinct proteins. (See page 3, first paragraph; mutant EGFRvIII has a deletion of amino acids 6 to 273 in the extra cellular region causing *constitutive* activation of tyrosine kinase domain) Given the fact that both EGFR and mutant EGFRvIII are functional different proteins, e.g. mutant EFGRvIII can cause constitutive activation of tyrosine kinase, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the instant recited antibody to detect cancers commensurate in scope with these claims.

In view of the quantity of experimentation necessary to determine the specific degree of carboxylation, the lack of direction or guidance presented, the absence of working examples, the breadth of the claims, and the unpredictability of the results, it would require undue experimentation for one skilled in the art to practice the entire scope of the claimed invention.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-11, 21-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

With respect to claim 1, line 1, "EGFRvIII" is vague and indefinite. Applicant is required to spell out the full name of EGFRvIII for clarity.

With respect to claim 2, applicant needs to spell out "CSF" context.

With respect to claim 24, it is not clear how this EGFRvIII specific antibody is rendered specific. It is not clear what is the relationship between the antibody and the absorption on one or more fragments of EFGR.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

9. Claims 1-9, 21-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wikstrand et al. (Cancer Res. 1997 57: 4130-4140) in view of Morgan et al. (US 5084396)

Wikstrand et al. teach assessing the qualitative distribution and quantitative expression of the EGFRvIII from neoplastic tissue samples, i.e. non-small cell lung carcinoma, and breast carcinoma (See abstract, Methods, and Table 3). The samples are from homogenized tumor cells, i.e. cell extracts, xenografing athymic mice and rats with the EGFRvIII transfected cell lines (See Method). The quantification of the EGFRvIII is conducted by use of EGFRvIII specific monoclonal antibody L8A4 (See abstract and Method). Wikstrand et al. also teach screening this EGFRvIII specific antibody in patients as an immunotherapeutic approach in combating lung, breast and central nervous cancers (page 3140, right column, second paragraph; page 3147, right column, last paragraph). For instance, Wikstrand et al. disclose using antibody-toxin conjugate, e.g. radio-iodinated antibody increasing killing of the cancer cells (page 3147, left column, second paragraph). Although Wikstrand et al. do not explicitly disclose using ELISA for measuring the EGFRvIII, Morgan et al. disclose that it is considered a *common practice* for incorporating ELISA assay in the art once the specific monoclonal antibody is available (Col. 5, line 55-60). Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have provided the EGFRvIII specific antibody developed by Wikstrand et al. with the ELISA assay as taught by Morgan et al to detect cancer with reasonable expectation of success since it is a common practice in the art for skilled artisan to measure the target protein once the specific antibody is

available and application of the specific antibody to ELISA involves routine practice in the art.

Response to Applicant's Arguments

10. The rejections of claims 1, 3, 5, 9, 11 over Wikstrand et al. in view of Morgan et al. are maintained.

Applicant argues that the prior art Wilkstrand et al. is distinguished from the current invention because Wilkstrand et al. do not teach using (1) ELISA assay and (2) an EGFRvIII specific antibody in measuring EGFRvIII in the sample. Applicant stresses that the instant invention contains a specific EGFRvIII antibody not disclosed in the teachings of Wilkstrand et al. (See Remarks, page 12, second and third paragraph) Applicant's arguments have been considered but are not persuasive. Examiner had discussed before in this Office Action that the secondary reference of Morgan et al. provided the motivation to apply the antibody to ELISA assay with a reasonable expectation of success. (See paragraph 9 in this Office Action) With respect to the argument on the specificity of the EGFRvIII, examiner would like to draw applicant's attention that Wilkstrand et al. also disclose EGFRvIII specific antibody by showing the reactivity of the isolated antibodies reacting with the target cells expressing EGFRvIII, but not A431 cells, which expresses only normal EGFR. (See Figure 2A and 2B; page 3143, left column, second paragraph; page 3146, left column, second paragraph) Therefore, Wilkstrand et al. do in fact teach a specific EGFRvIII antibody.

11. Applicant's arguments with respect to claims 6 have been considered but are moot in view of the new ground(s) of rejection. (See above)

Conclusion

12. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jacob Cheu whose telephone number is 571-282-0814. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jacob Cheu
Examiner
Art Unit 1641

June 15, 2004

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SUPERVISORY PATENT EXAMINER
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06/24/04